Addison's disease in dogs: typical and atypical presentations

Reusch, Claudia E

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Claudia E. Reusch
Prof. Dr., Dipl ECVIM-CA
Clinic for Small Animal Internal Medicine, University of Zurich, Switzerland

Naturally occurring hypoadrenocorticism is a relatively rare endocrine disorder in the dog. The vast majority of cases suffer from primary hypoadrenocorticism which is also known as Addison's disease (AD). It is currently assumed that the major cause is autoimmune destruction of the adrenal glands; other causes are bleeding, infarct, infiltrative destruction due to abscesses, neoplasia or granulomatous disease. At least 90% of adrenocortical tissue has to be destroyed before clinical signs become apparent. In immune mediated AD tissue loss usually takes place in a slow and progressive manner over weeks to months. Typically, the destruction terminates in absolute deficiencies of glucocorticoids and mineralocorticoids with high levels of endogenous ACTH due to negative feedback.
The disease may occur at any age, most often young-middle aged dogs are affected. There is a female predisposition and there is also a genetic predisposition in some breeds (e.g. Bearded Collie, Standard poodle, Portuguese water dog, Nova Scotia Duck Tolling Retriever). The presentation may be an emergency because of sudden onset of serious problems (so called Addison crisis) such as anorexia, lethargy, weakness, collapse, dehydration, hypotension and bradycardia (absolute or relative). In those dogs the initial symptoms may have been mild and not taken seriously by the owner. Alternatively, the dog may be presented due to chronic illness with symptoms such as intermittent lethargy, weight loss, weakness, pu/pd, vomiting.
20 to 30% of dogs with AD reveal a mild to moderate normochromic, normocytic anemia. A hematocrit < 20% may be seen in dogs with severe gastrointestinal hemorrhage. Usually, patients do not have a stress leucogram, eosinophilia and/or lymphocytosis is present in 10-20%. The *typical* or "classical" laboratory abnormalities are hyperkalemia and/or hyponatremia; hyperkalemia occurs in about 90% and hyponatremia in about 80% of cases. The severity of the electrolyte alterations range from subtle to very severe and life-threatening. It should be remembered that although hyponatremia and hyperkalemia are often seen in dogs with AD, they are not specific for the disease. In about 10% of dogs with AD sodium and potassium concentrations are within the normal range, which has been referred to as *atypical AD.* In those dogs diagnosis may be delayed because the *typical* alterations are lacking and therefore the index of suspicion is low. Various authors have postulated that in those dogs the destructive (e.g. immune-mediated) process is confined to the zones fasciculata/reticularis leading to an isolated glucocorticoid deficiency with intact aldosterone secretion. However, so far there are no histological studies confirming that the zona glomerulosa is intact and in most studies aldosterone was not measured. We recently investigated cortisol and aldosterone concentrations pre and post ACTH (i.e. during an ACTH stimulation test) in healthy dogs, dogs with diseases mimicking AD and in dogs with AD. Healthy dogs and dogs with mimicking diseases showed a significant increase in cortisol and aldosterone post ACTH, which was lacking in dogs with AD. Interestingly, 67 of the 70 dogs with AD had low-undetectable aldosterone concentrations independent of the degree of electrolyte abnormalities. In 5 of the 67 dogs the so-called *atypical AD* was present, i.e. the electrolytes were normal (without aldosterone!). According to our results it seems likely that also in "atypical" AD the zona glomerulosa is destroyed and that in those dogs other mechanisms (most likely of renal origin) are able to maintain normal electrolytes. Azotemia is common in dogs with AD and is attributable to hypovolemia and hypotension due to decreased renal perfusion and GFR. Normally, the determination of urine specific gravity is used to differentiate between prerenal and renal azotemia; in prerenal azotemia it is greater than 1.030. Although dogs with AD have prerenal azotemia, more than 2/3 of these dogs have a urine specific gravity of less than 1.030. Therefore, these cases initially cannot be

differentiated from those with primary renal insufficiency. In about 50% of dogs hypoalbuminemia is present, which is associated with gastrointestinal loss and may be severe, 30% demonstrate hypercalcemia and 20% hypoglycemia.
The ACTH stimulation test is the test of choice to confirm AD. Dogs with AD reveal no or only very little increase of cortisol 1 hour after the application of synthetic ACTH (usually cortisol is < 2 µg/dl, 55.2 nmol/l). Additional measurement of cACTH enables differentiation between AD and secondary hypoadrenocorticism, which is of particular importance in dogs with normal sodium and potassium concentrations. In dogs with AD cACTH is highly increased, whereas it is low in secondary hypoadrenocorticism. As mentioned above aldosterone concentrations usually are low in dogs with AD and are therefore of no additional diagnostic value.
The extent of therapy depends on the clinical status of the animal and the degree of laboratory abnormalities (in particular degree of hyperkalemia). Rapid correction of hypovolemia has the highest priority. The fluid of choice is 0.9% saline solution which does not contain potassium. The amount and rate of infusion depends on the degree of dehydration, extent of ongoing losses and urine output. As a rough guideline an initial rate of 60 – 80 ml/kg/h can be used for the first 1 – 2 hours. Thereafter the fluid rate can be decreased to 2 – 3 times maintenance which should be used for 36 – 48 hours. In most dogs clinical signs resolve within the time period and infusion therapy can be slowly diminished. Fluid therapy results in marked reduction in serum potassium, restoration of renal perfusion and correction of metabolic acidosis. A rapid increase in serum sodium concentration has been associated with neurological signs caused by myelinolysis. Although this complication is rare, in dogs with severe hyponatremia treatment should be adjusted so that serum sodium concentration does not increase by more than 0.5 mmol/l/h. Most often specific treatment for hyperkalemia is not needed, because it is corrected by appropriate fluid therapy. Severe hyperkalemia may be treated by IV glucose (1-2ml/kg of the 50% glucose solution dilute if application is through peripheral vein). After finishing the ACTH test IV glucocorticoids should be given (e.g. methylprednisolone sodium succinate, 2-3 mg/kg). Usually, the application of mineralocorticoids can be delayed until the patient has been stabilised and oral medication is possible. Alternatively, DOCP (Percorten-V) a depot mineralocorticoid which is applied as SC injection can be started immediately after the ACTH test. Long term therapy consists of mineralocorticoid and glucocorticoid supplementation. As mineralocorticoids either DOCP (Percorten-V) or fludrocortisone can be used. DOCP is given as SC injection (initial dose 1.8 – 2.0 mg/kg) every 25 days, time intervals may be prolonged in many dogs. Fludrocortisone is given orally at an initial dose of 0.015 – 0.02 mg/kg/day (split into 2 doses). Glucocorticoid supplementation is needed in all dogs treated with DOCP and in approximately 50% of dogs treated with fludrocortisone. Initial dose is 0.1 – 0.2 mg/kg of prednisolone, in times of severe stress a 2 – 10 fold increase may be required. Dogs with normal sodium and potassium concentrations do not need mineralocorticoid replacement. However, since they usually have low aldosterone concentrations and may develop electrolyte changes later in the course of the disease close supervision is needed.
During the first 3 months we re-evaluate dogs every 1 – 3 weeks, thereafter twice per year.

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